APPENDIX D.

DESCRIPTION OF PROPOSED STUDY

GENE THERAPY FOR RECURRENT PEDIATRIC BRAIN TUMORS

In an attempt to improve the grim prognosis associated with malignant pediatric brain tumors, a novel therapeutic approach to these tumors is being investigated. This approach uses recombinant DNA technology to transfer a gene which confers sensitivity to an antiviral drug into the tumor. This is achieved by direct injection of the tumor with cells which actively produce a retroviral vector carrying the sensitivity gene. The agent of transfer, or vector, is a retrovirus which has been modified so that it cannot reproduce itself. Such vectors are capable of stably incorporating their genetic material into the DNA of the host. The producer cell is an NIH 3T3 (mouse fibroblast) cell that has been genetically engineered to continually produce retroviral vectors. The vectors are inserted into dividing cells. Since normal brain cells are not actively growing or dividing, insertion of the producer cells into a brain tumor will result in vectors entering only the proliferating tumor cells. The vectors incorporate their DNA into the tumor cells, including the drug sensitivity gene. The gene leads the tumor cells to express a protein (herpes simples virus enzyme thymidine kinase or HS-tk) that sensitizes the cells to an antiviral drug (ganciclovir or GCV). When GCV is administered systemically, cells expressing the HS-tk protein convert GCV into a toxic substance intracellularly that leads to the death of the affected cells. Normal human cells inside and outside the brain are not sensitive to GCV. The selective uptake of the vector, therefore, allows specific cell kill of the affected tumor cells while sparing the adjacent normal brain cells and the cells outside the brain. This type of gene transfer has several unique features. First, these retroviral vectors only integrate and express their genes in cells which are actively synthesizing DNA. The brain in unique because normal brain cells are not mitotically active in children beyond 2 years of age. Therefore, only the actively dividing tumor cells are expected to express the HS-tk enzyme and become target for GCV; surrounding non-proliferating normal brain tissue should not acquire the HS-tk gene and will remain insensitive to GCV. Second, all of the transduced tumor cells (and retroviral vector producing cells) will be killed by the host immune response and/or GCV treatment, eliminating potential concern about vector-related changes giving rise to malignant cells in the tumor region or elsewhere.